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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-335/S-003**

**Clinical Pharmacology and Biopharmaceutics  
Review**

## **Clinical Pharmacology & Biopharmaceutics Review**

### **I. Project Identification**

- |                             |  |
|-----------------------------|--|
| 1. NDA number/serial number | 21,335/SE8-003-BB  |
| 2. Submission date          | August 26, 2002  |
| 3. Drug name                | Gleevec  |
| 4. Generic name             | imatinib mesylate  |
| 5. Dosage form              | 50 and 100 mg capsules   |
| 6. Sponsor                  | Novartis Pharmaceutical Corporation<br>One Health Plaza<br>East Hanover, NJ 07936-1080 |
| 7. Reviewer                 | Anne Zajicek, M.D., Pharm.D.   |
| 8. Type of Submission:      | NDA-general (minor amendment)  |

### **II. Purpose**

The purpose of this minor amendment is to submit, in electronic version, the narrative portions of Gleevec Study 103 (A phase 1, dose finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles and to evaluate for anti-leukemic effects of STI571 in pediatric patients with Ph+ leukemia) and Study 03-001 (A phase 1, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles, and to evaluate for preliminary antileukemic effects).

### **Comments**

The Clinical Pharmacology and Biopharmaceutics reviewer appreciates the availability of the submission in electronic format.

### **Recommendations**

No action is indicated.

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Anne Zajicek, M.D., Pharm.D.

N.A.M. Atiqur Rahman, Ph.D.

CC: NDA 21,335  
HFD-150 Division File  
HFD-150 AStaten  
HFD-150 Jjohnson, Pbross, AShapiro  
HFD-860 MMehta, CSahajwalla, ARahman, AZajicek  
CDR Biopharmaceutics

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BIOPHARMACEUTICS

## **Clinical Pharmacology & Biopharmaceutics Review**

### **I. Project Identification**

1. NDA number/serial number      21,335/SE8-003-BM
2. Submission date                      November 13, 2002
3. Drug name                              Gleevec
4. Generic name                          imatinib mesylate
5. Dosage form                            50 and 100 mg capsules
6. Sponsor                                  Novartis Pharmaceutical Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080
7. Reviewer                                Anne Zajicek, M.D., Pharm.D.
8. Type of Submission:                  NDA-general (minor amendment)

### **II. Purpose**

The purpose of this minor amendment is to submit formally the email exchanged between Novartis and the reviewer and team leader from the Office of Clinical Pharmacology and Biopharmaceutics, in response to various questions (mostly involving the assay) which arose in the course of the review of Gleevec NDA21,335/s003 —

### **III. Comments**

Email from Novartis to the reviewer, in response to specific review questions, is presented (see Appendix 1).

### **IV. Recommendations**

No action is indicated.

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Anne Zajicek, M.D., Pharm.D.

N.A.M. Atiqur Rahman, Ph.D.

CC: NDA 21,335

**HFD-150 Division File**

**HFD-150 AStaten**

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**CDR Biopharmaceutics**

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BIOPHARMACEUTICS



## **Clinical Pharmacology and Biopharmaceutics Review**

NDA: 21335/S-003  
Drug: Gleevec  
Generic Name: imatinib mesylate  
Formulation: 50 and 100 mg capsules

Proposed indication: Philadelphia chromosome positive (Ph<sup>+</sup>) CML in children

Applicant: Novartis Pharmaceutical Corporation  
59 Route 10  
East Hanover, N.J. 07936

Submission date: June 28, 2002  
Reviewer: Anne Zajicek, M.D., Pharm.D.  
Medical Officer  
Office of Clinical Pharmacology and  
Biopharmaceutics

Pharmacometric Team Leader: Joga Gobburu, Ph.D.

Team Leader: N.A.M. Atiqur Rahman, Ph.D.

Type of submission: NDA/Supplemental

This is a review of the clinical pharmacology and biopharmaceutics studies submitted in supplement 003 to NDA 21-335 in support of a new pediatric indication for Gleevec, for the treatment of pediatric Philadelphia chromosome positive (Ph<sup>+</sup>) leukemia.

### **I. Executive Summary**

The applicant has submitted one study in Section 6 (Human Pharmacokinetics and Bioavailability) of the NDA to seek approval for a new indication for Gleevec, for the treatment of children with Ph<sup>+</sup> leukemia. The recommended dose from the applicant is 260 mg/m<sup>2</sup> for the chronic phase, and 340 mg/m<sup>2</sup> for the accelerated or blast crisis phases of chronic myelogenous leukemia.

### **A. Overall recommendations**

The clinical pharmacology and biopharmaceutics information submitted in the sNDA for GLEEVEC<sup>™</sup> is acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics. The pharmacokinetic studies submitted give adequate information to evaluate the pharmacokinetics of imatinib in children, which appear to be similar to adults. Further evaluation of efficacy and safety of the 260 mg/m<sup>2</sup> dosage recommendation should be considered as a Phase 4 commitment since this dose produced the same exposure (AUC) as the 340 mg/m<sup>2</sup> dose. The 50 mg capsule strength must be marketed by the applicant to provide suitable doses for children.

## B. Comments

There are remaining questions about the assay validation methods used by the applicant, including elements regarding sample stability. The pediatric data come from Studies 0103 and 03 001 using non-cross validated assays. There appears to be a considerable amount of accumulation (22 % of the AUC of the imatinib) of the equipotent metabolite CGP74588 with chronic dosing; the protein binding of the metabolite has not yet been measured so the clinical significance of these increased concentrations is unclear.

## C. Labeling comments

### II. Special Populations

#### Applicant proposal:

##### *Pediatric*

#### FDA response:

*Pediatric:* As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a C<sub>max</sub> of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m<sup>2</sup> in children vs 10.0 L/hr/m<sup>2</sup> in adults), as was the half life (14.8 hours in children vs 17.1 hours in adults). L

levels revealed a 1.5 and 2.2 -fold drug accumulation, respectively after repeated once daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

/S/

/S/

Reviewer: Anne Zajicek, M.D., Pharm.D. Team Leader: N.A.M. Atiqur Rahman, Ph.D.

CC: NDA 21,335/

HFD-150/ Division File

HFD-150/StatenA, ShapiroA, JohnsonJ

HFD-860/MehtaM, SahajwallaC, RahmanN, ZajicekA

CDR/Biopharm

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### III. List of Abbreviations

AUC: area under the concentration vs. time curve  
AUC<sub>0-∞</sub>: area under the concentration-time curve extrapolated from time 0 to infinity  
BSA: body surface area  
C<sub>max</sub>: peak plasma concentration of the drug  
CL: clearance  
CL/F: apparent oral clearance  
CML: chronic myelogenous leukemia  
CV: coefficient of variation  
CYP450: cytochrome P-450  
GIST: gastrointestinal stromal tumor  
Hr, hrs: hours  
Kg, kg: kilograms  
K<sub>i</sub>: constant of inhibition  
L: liter  
LOD: lower limit of detection  
LOQ: lower limit of quantification  
M<sup>2</sup>, m<sup>2</sup>: square meters, meters squared  
Min, min: minutes  
ml, mL: milliliter  
μg/L: micrograms per liter  
μM: micromolar, micromoles per liter  
NDA: New Drug Application  
ng/ml: nanograms per milliliter  
PD: pharmacodynamics  
PDGF-R: platelet-derived growth factor receptor  
Ph<sup>+</sup>: Philadelphia chromosome positive  
PK: pharmacokinetics  
PPK: population pharmacokinetics  
sNDA: supplemental NDA  
T<sub>1/2</sub>, t<sub>1/2</sub>: half-life V<sub>z</sub>/F: apparent volume of distribution  
T<sub>max</sub>: time to reach maximal concentration  
t(9,22): translocation between chromosomes 9 and 22  
V: volume of distribution

#### IV. Summary of clinical pharmacology findings

Imatinib in children demonstrated rapid oral absorption, with a  $t_{\max}$  ranging from 2 to 4 hours. The apparent oral clearance values averaged  $6.63 \text{ L/h/m}^2$  ( $11.5 \text{ L/h/1.73 m}^2$ ) on Day 1, and  $6.38 \text{ L/h/m}^2$  ( $11.0 \text{ L/h/1.73 m}^2$ ) on Day 8. There was large interpatient variability in area under the curve (AUC). The mean AUC did not increase proportionally with dose within the range of doses administered, in contrast to adults.

Pediatric pharmacokinetic values are similar to adult values. Steady-state clearances were  $11.0 \text{ L/h/1.73m}^2$  in children, compared with  $10.0 \text{ L/hr/1.73 m}^2$  in adults. The half-life ( $t_{1/2}$ ) was 14.8 hours in children, and 17.1 hours in adults.

The pharmacokinetics (PK) of imatinib could not be correlated with the pharmacodynamics (PD), due (perhaps) to the small number of patients evaluated. Also the pharmacokinetics of the active metabolite of imatinib (CGP 74588) was not assessed and correlation with the PD explored.

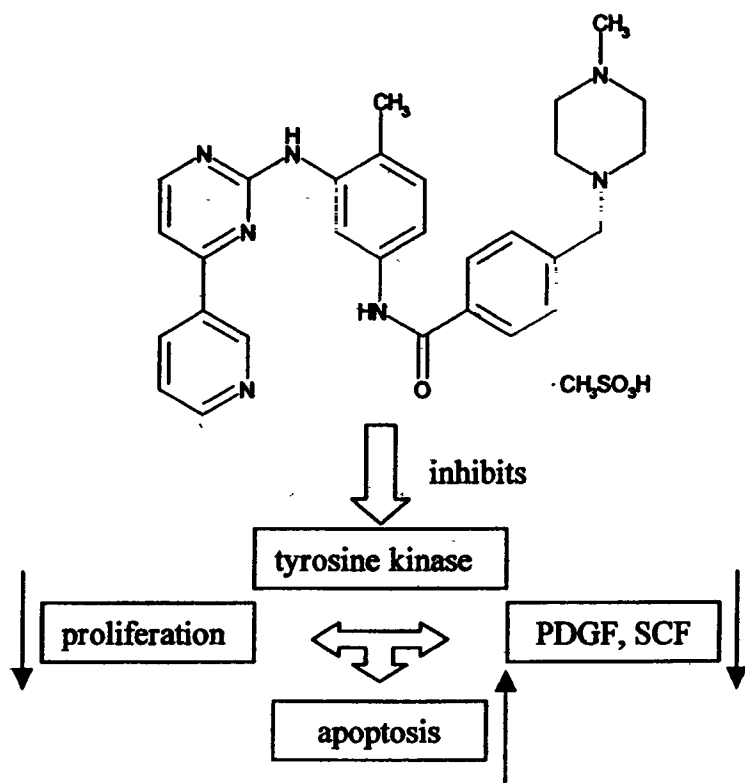
The pediatric dosing recommendation by the applicant of  $260 \text{ mg/m}^2$  for the chronic phase of CML, and  $340 \text{ mg/m}^2$  for the advanced and blast crisis phases of CML, are similar to adult recommendations on a body surface area basis. The AUCs for the  $260 \text{ mg/m}^2$  and for the  $340 \text{ mg/m}^2$  dose are both similar to the adult  $400 \text{ mg}$  dose.

The drug may be dissolved in water or apple juice, with good dissolution and short term (4 hr) stability. The drug may not be dissolved in Coca-Cola or orange juice

#### V. Background

##### Mechanism of action

Imatinib mesylate (molecular weight 589.7, see Figure 1 below) is a novel chemotherapeutic agent, which binds to and inactivates the bcr-abl tyrosine kinase fusion protein produced by translocation of chromosomes 9 and 22 (t(9;22), the Philadelphia chromosome). This mutation causes Philadelphia chromosome positive ( $\text{Ph}^+$ ) chronic lymphocytic leukemia.



Imatinib inhibits platelet derived growth factor receptor (PDGF-R) tyrosine kinase signaling. It also inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells which express an activating c-kit mutation.

Imatinib was approved in 2001 by FDA for use in  $\alpha$ -interferon (IFN)- refractory  $\text{Ph}^+$  CML, and in early 2002 for c-kit positive GIST. It was most effective in inducing remission for patients in the chronic phase of CML (93 %), and to a lesser extent in the accelerated phase (37 %) and blast crisis phase (5 %).

Imatinib is administered orally once or twice daily. Common side effects include nausea, fluid retention which is occasionally severe, muscle cramps, diarrhea, vomiting, hemorrhage, fatigue, and arthralgias. In adults treated with imatinib, advanced age and edema were correlated: older patients (> 60 years old) were more likely to have higher grades of edema than younger patients.

#### Pharmacokinetics in adults:

**Absorption:** Imatinib is rapidly and well absorbed, with a  $t_{\text{max}}$  of 2-4 hours, and an oral bioavailability of approximately 98 %. There appears to be dose-proportionality in the dose range of 25-1000 mg, but with a large variability (>40 %) in AUC. Relative bioavailability for a solution of imatinib compared to the intact capsule was 98.8 % (90 % confidence interval 87.7-111 %).

**Distribution:** Imatinib is 89-96 % protein bound, primarily to albumin and  $\alpha_1$ -acid glycoprotein. The protein binding is concentration dependent; concentrations in plasma of — ng/ml were 95 % bound, a concentration of — ng/ml was 91 % bound, — ng/ml were 86 % bound. Concentrations less than — ng/ml are the most relevant clinically; therefore, in the clinically relevant range, imatinib is 91-96% bound. Volume of distribution of imatinib is large, at 244.2 L/80 kg, with a coefficient of variation (CV) of 31 %. The protein binding of the N-desmethyl metabolite is unknown.

**Metabolism:** Clearance is primarily hepatic, by the cytochrome P450 (CYP) enzyme system. CYP3A4 is the specific isozyme which metabolizes imatinib. Clearance averaged 10.0 l/hr/70 kg, with a large interpatient variability (CV 32 %). The half-life of imatinib averages approximately 18 hours.

Studies with human liver microsomes demonstrated that imatinib is a potent competitive inhibitor of CYP 2C9, 2D6, and 3A4/5. The potential therefore exists for imatinib to inhibit the metabolism of compounds metabolized by these enzymes, such as S-warfarin (2C9 substrate), desipramine (2D6), and simvastatin (3A4).

In a clinical study, imatinib increased the AUC of simvastatin by 3.5 fold. Conversely, a single dose of ketoconazole, a CYP 3A4 inhibitor, increased the AUC of imatinib by 40 %. A case report indicated that phenytoin (a potent CYP3A4 inducer) co-administration produced suboptimal response to, and decreased concentrations of, imatinib; this effect was reversed when phenytoin was stopped.

There is a single active metabolite, N-desmethyl imatinib, or CGP74588, which has equal *in vitro* activity with the parent compound; however, the AUC of CGP74588 is about 16 % of the AUC of imatinib in the adults studied. Its  $t_{1/2}$  is approximately 40 hours. CGP74588 inhibits its own formation with a  $K_i$  value of 21  $\mu\text{M}$  ( — ng/ml), and, like imatinib, also inhibits substrates of 2C9, 2D6, and 3A4/5.

**Elimination:** When  $^{14}\text{C}$ -labeled imatinib was administered orally, 81 % of the dose was eliminated within 7 days, with 68 % excreted in the feces and 13 % in the urine. Unchanged imatinib accounted for 25 % of the dose collected (5 % in urine, 20 % in feces); CGP74588 accounted for 11 % of the dose eliminated as metabolites.

## VI. Question-based review of Gleevec (imatinib mesylate)

### A. Do the pharmacokinetics of Gleevec in children differ from those in adults?

A Phase 1 study (Study 0103) with 31 children aged 3-19 years who were diagnosed with  $\text{Ph}^+$  leukemias, including CML, and acute leukemias with myeloid and lymphoid morphology, was conducted. Pharmacokinetics of imatinib were studied in 27 of these patients. The children were treated with escalating doses of imatinib (260, 340, 440, and 570  $\text{mg}/\text{m}^2$ ), administered once daily ( $n=22$ ) or twice daily ( $n=5$ ). Pharmacokinetics of imatinib and CGP74588 were determined on Day 1 and Day 8 of treatment. In addition, the pharmacokinetics were studied in 6 additional children, who received once daily imatinib, from study 03-001 in the original NDA submission.

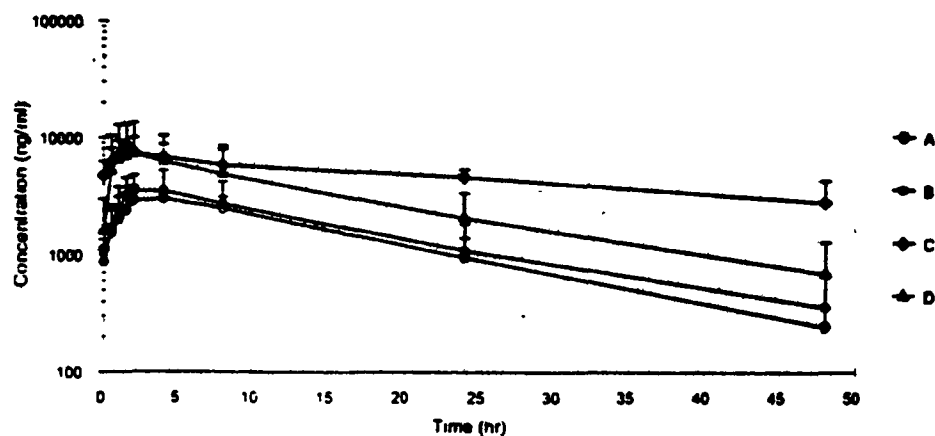
Table 1 shows the pharmacokinetic parameters of patients in Study 103 after their first dose of imatinib. There is a large interpatient variability in the time course of drug concentrations, and pharmacokinetic parameters.

**Table 1. Pharmacokinetic parameters of imatinib in children on Day 1**

Dose/day (mg/m <sup>2</sup> )	No of patients		t <sub>max</sub> (h)	C <sub>max</sub> (ng/ml)	t <sub>1/2</sub> (h)	AUC <sub>(0-24)</sub> (ng.h/ml)	AUC <sub>(0-∞)</sub> (ng.h/ml)	V <sub>z</sub> /F (L)	Cl/F (L/h)
Once daily dose									
260	6	mean	3.5	3624.5	8.9	50988.4	60582.7	118.9	8.9
		SD	2.5	1982.8	1.2	34873.2	39723.2	83.4	5.8
340	8	mean	3.7	2475.0	9.2	32113.6	39613.4	167.4	12.8
		SD	2.1	943.9	1.9	13097.1	17430.3	84.4	6.8
440	4	mean	5.0	5392.5	12.8	76076.6	103302.0	189.7	9.3
		SD	2.0	4280.3	2.5	54815.2	64806.2	213.1	9.4
570	4	mean	2.9	8537.5	14.8	106697.6	150749.1	109.1	5.6
		SD	1.3	9190.3	12.9	113574.2	133125.3	87.6	2.8
Twice daily dose									
340	1		24.0	2720.0	Missing	37032.2	Missing	Missing	Missing
440	1		13.0	1830.0	18.7	29103.0	60118.8	179.5	6.7
440	1		2.0	2610.0	Missing	30866.5	Missing	Missing	Missing
570	1		16.0	11200.0	16.5	186753.1	377909.4	28.4	1.2
570	1		4.0	3030.0	36.6	53085.1	160276.0	164.7	3.1

Figure 2 and Table 2 show the time course and PK parameters in children following dosing on Day 8. In comparison to Day 1 values, the Day 8 mean AUC was increased, the apparent oral clearance was decreased in comparison (9.2  $\text{L}/\text{hr}$  to 7.48  $\text{L}/\text{h}$ ), and half-life was increased.

**Figure 2. Mean  $\pm$  SD plasma concentrations of imatinib at steady state after once daily administration (A: 260 mg/m<sup>2</sup>, B: 340 mg/m<sup>2</sup>, C: 440 mg/m<sup>2</sup>, D: 570 mg/m<sup>2</sup>)**



**Table 2. Pharmacokinetic parameters of imatinib in children on Day 8**

Dose (mg) /m <sup>2</sup>	No of patients		t <sub>max</sub> (h)	C <sub>max</sub> (ng/ml)	C <sub>min</sub> (ng/ml)	t <sub>1/2</sub> (h)	AUC <sub>(0-24)</sub> (ng.h/ml)	AUC <sub>(0-∞)</sub> (ng.h/ml)	Vz/F (L)	CVF (L/h)
Once daily dose										
260	6	mean	3.3	3301.3	849.3	11.7	48611.0	67314.4	136.2	7.9
		SD	1.0	658.5	357.8	1.9	10407.2	18181.3	54.0	2.4
340	8	mean	2.3	4012.5	744.8	13.0	54982.8	80368.2	166.9	9.7
		SD	1.1	1535.4	668.4	3.7	26431.7	43872.1	74.7	5.3
440	4	mean	8.9	9420.0	4037.5	23.2	136690.0	308841.5	154.0	4.6
		SD	10.5	3982.7	971.7	11.9	33390.0	71692.7	107.7	1.6
570	4	mean	2.4	7592.5	1544.2	13.6	103071.4	150776.9	131.6	6.9
		SD	1.1	5939.3	1359.9	2.9	69612.5	103958.8	73.1	3.9
Twice daily dose										
340	1		3.0	3170.0	1910.0	18.5	53195.0	103289.6	388.8	14.6
440	1		10.0	3840.0	2080.0	17.5	78355.0	148227.2	260.3	10.3
440	1		4.0	4280.0	2170.0	18.9	81355.0	183657.2	278.5	10.2
570	1		2.0	10900.0	1750.0	11.3	140575.0	215850.7	85.6	5.3
570	1		1.0	5430.0	997.0	70.5	110203.5	570700.9	947.9	9.3

#### **Comparison with adult pharmacokinetic parameters:**

Study 106, an adult study using Gleevec as first-line treatment for newly diagnosed CML, was submitted at the same time as this pediatric study. It presents a population



pharmacokinetic (PPK) study of 371 adults treated with once daily imatinib; PK studies using sparse sampling were performed on Days 1 and 29 of treatment.

Pharmacokinetic results of this PPK study show a clearance of 13.8 L/hr/80 kg, on Day 1, and 10.0 L/hr/70 kg on Day 29. Assuming that an 80 kg adult has a body surface area of 1.73 m<sup>2</sup>, these values correspond to 7.98 L/h/m<sup>2</sup> and 5.78 L/h/m<sup>2</sup>, respectively. These values are similar to the pediatric values of 6.63 L/hr/m<sup>2</sup> on Day 1 and 6.38 L/h/m<sup>2</sup> on Day 8. Table 3 compares pediatric and adult pharmacokinetic parameters.

**Table 3. Comparison of Pharmacokinetic Parameters between Children and Adults**

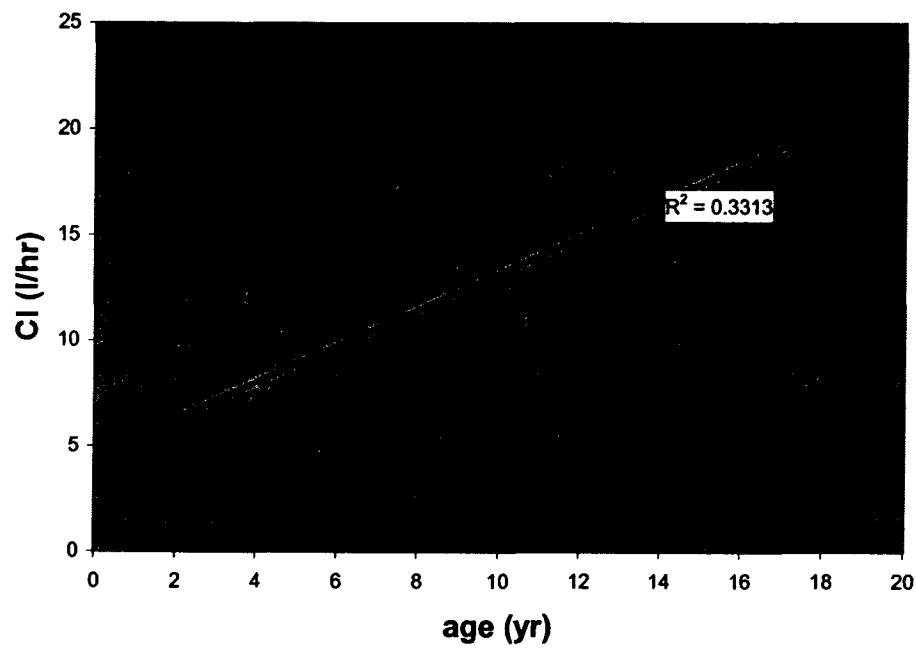
Pharmacokinetic Parameters	Pediatrics Mean (CV%)	Adults Mean (CV%)
Cl/F (L/hr/m <sup>2</sup> )	6.38 (48 %)	5.78 (32 %)
V <sub>z</sub> /F (L/m <sup>2</sup> )	112.7 (38 %)	244.2 (31 %)
t <sub>1/2</sub> (hr)	14.8 (39 %)	17.1

**B. Is there a relationship between age and clearance in children ?**

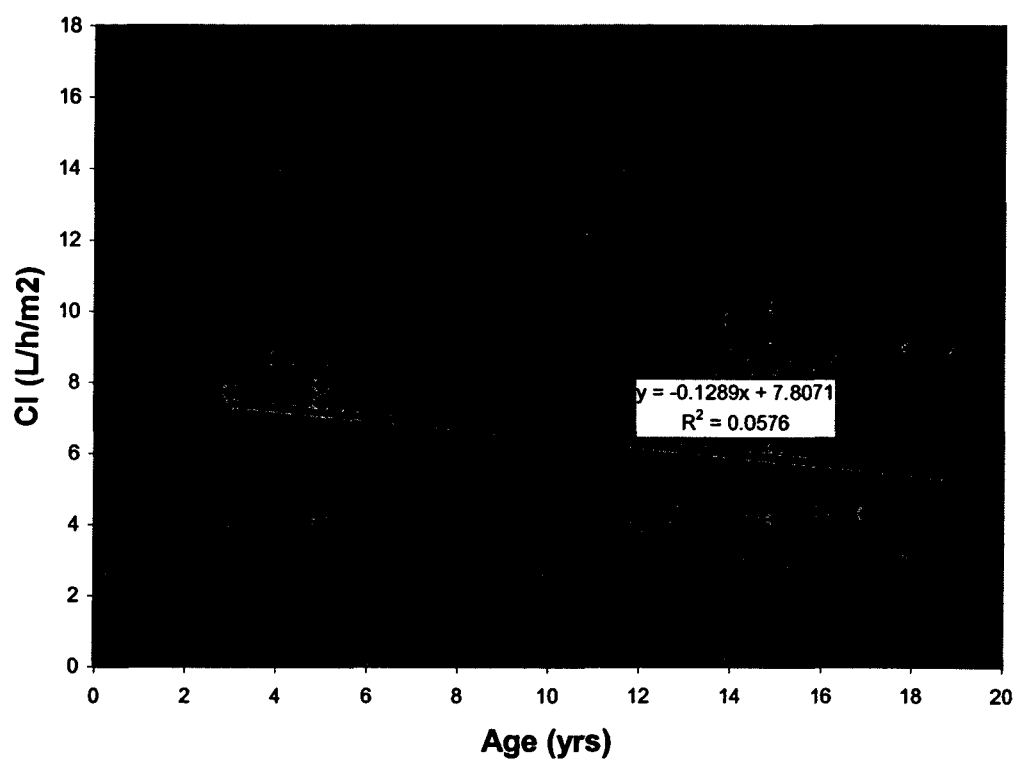
There was a linear relationship between age and unnormalized clearance (See Figure 3). The coefficient of determination was 0.58, indicating that 58 % of the variability in clearance can be explained by age. Figure 4 is a plot of normalized clearance and age, where clearance is normalized to body surface area. Clearance is relatively unchanged over the age range 3-20 years. Table 4 shows PK parameters for three different age groups (2 to <12, 12 to <18, and ≥ 18 years) as the applicant had stratified the pediatric patients for safety and efficacy. By both visual inspection and statistics, there is no difference among the age groups for any PK parameters.

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**Figure 3. Unnormalized Clearance as a Function of Age**



**Figure 4. Normalized Clearance as a Function of Age**



**Table 4. Pediatric pharmacokinetic parameters stratified by age**

Pharmacokinetic Parameter (mean $\pm$ SD)	2 to < 12 years mean $\pm$ SD	12 to < 18 years mean $\pm$ SD	> 18 years mean $\pm$ SD
$t_{\max}$ (hr)	3.04 (1.78)	4.68 (6.47)	2.38 (1.11)
Cl/F (L/hr/m <sup>2</sup> )	7.10 (3.57)	5.40 (2.38)	6.75(2.70)
$V_z/F$ (L/m <sup>2</sup> )	109 (51.5)	107.3 (36.4)	138.6 (23.9)
$t_{1/2}$	14.17 (4.92)	14.50 (2.78)	17.75 (12.75)

**C. Is there accumulation ?**

The accumulation factor is calculated by taking the ratio of  $AUC_{0-\infty}D8/AUC_{0-\infty}D1$ . For imatinib, the accumulation factor averaged 2.16 (SD 1.76, range — ), indicating that the AUC of imatinib at steady state was approximately 116% higher than the AUC after the first dose.

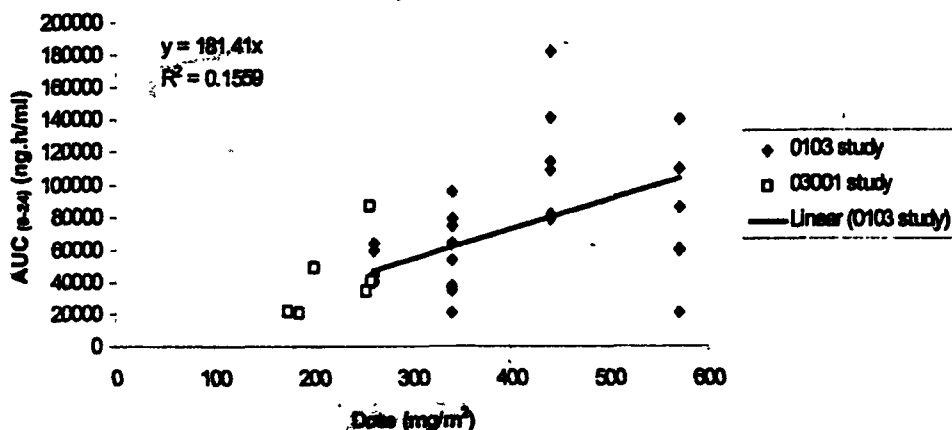
The accumulation factor for the metabolite, which has a significantly longer half-life than the parent compound, is 4.54; this indicates significant accumulation of the equipotent metabolite at steady-state.

The ratio of parent to metabolite on Day 1 is 6.4, but decreases to 3.46 by Day 8. This indicates that there is relatively little metabolite initially (the exposure to the metabolite is  $\approx$ 14 % of the exposure to parent drug), but by Day 8 the exposure to the metabolite has increased considerably (exposure to metabolite is now 22 % of exposure to parent compound). The protein binding of the metabolite is not known, so the true clinical significance of this metabolite accumulation is unclear. However, if the metabolite is significantly less protein bound, this increased exposure could produce a clinical effect.

**D. Is there dose-proportionality ?**

No. The applicant presented this figure (Figure 5) to demonstrate the relationship between area under the curve and dose from all of the pediatric patients who received once daily imatinib. There is no relationship between dose, normalized to either weight or body surface area, and AUC.

**Figure 5. Lack of Relationship between Dose (normalized to body surface area) and Exposure**



**E. Is there a PK-PD relationship ?**

No. In the submission presented, pharmacodynamic effects were explored by examining the relationship between WBC counts after 28 days of treatment and drug exposure (AUC). Unlike the results in adults, there was no clear correlation between drug exposure and normalization of WBC counts.

**F. Were all patient samples measured by the same assay?**

Two non-cross-validated assays were used to measure imatinib plasma concentrations. Each was independently validated. Both methods, (assay B) and (assay C), used methods, with and a range of quantification of ng/ml. The methods differed in sample preparation. Method while Method used. Samples from Study 03 001 (from the original NDA submission) and samples from the first three patients enrolled in Study 0103 were assayed by the first method, and the specimens from the remaining 19 of 22 patients from Study 0103 were measured by the second method. Sample stability was not addressed in their assay validation.

The issue of lack of cross-validation questions the ability to use all pediatric data together; in other words, can samples measured by different assays be treated as a single data set or should they be separated by assay method ? In order to address this question, patient data was separated by assay method, and a t-test was used to determine if the sample concentrations were different from each other. Table 5 below stratifies imatinib pharmacokinetic results by assay, for all children treated with once-daily imatinib. There was no statistical difference between PK results for Assays B or C.

	Table 5. Comparison of Patient Parameters Stratified by Assay			
	All (+ SD)	Assay B (+ SD)	Assay C (+ SD)	p value (Assay B vs C)
Age (yr)	11.07 (5.65)	10.56 (5.17)	11.32 (5.98)	0.37
Cl/F (L/h/m <sup>2</sup> ) Day 1	6.63 (3.68)	6.92 (2.09)	6.48 (4.32)	0.36
Cl/F (L/h/m <sup>2</sup> ) Day 8	6.38 (3.04)	6.25 (2.22)	6.44 (3.41)	0.43
Cl/F (L/h) Day 1	9.21 (6.09)	8.01 (2.89)	9.81 (7.18)	0.18
Cl/F (L/h) Day 8	7.56 (3.8)	7.1 (2.37)	7.77 (4.36)	0.3
t 1/2 (h) Day 1	10.32 (5.41)	9.24 (3.28)	10.87 (6.22)	0.19
t 1/2 (h) Day 8	14.82 (5.84)	15.47 (4.79)	14.5 (6.42)	0.33

The pharmacokinetic parameters from Assay B and Assay C are not statistically different from each other. Therefore, these assays appear equivalent, and the data can be pooled.

#### **G. Is the presented dissolution/stability data for dissolving the capsules in H<sub>2</sub>O or apple juice valid ?**

Yes, the dissolution data is valid.

A study was done to determine dissolution and stability of the opened capsule contents in various liquids, in order to provide a suitable drug delivery form for children who are unable to swallow capsules. Capsule contents were emptied into a variety of liquids (water, apple juice, orange juice, Coca-Cola), and concentrations of imatinib were measured at 0 (immediately after mixing), 4, and 24 hours. Acceptable results were those that showed concentrations no less than 2 % below the starting value of the measured drug concentration.

Water and apple juice showed acceptable dissolution and short-term stability results. Water showed acceptable results at time 0 and 4 hours, apple juice at 0, 4, and 24 hours. Orange juice and Coca-Cola showed unacceptable results. For orange juice, the start concentration was already below limit of acceptability (86.5-87.5 %), and remained at that level at 4 hours (86.3-86.7 %) and 24 hours (85.8-86.0 %). This may have been due to drug adsorption to the fruit residues. There was strong discoloration of the brown Coca-Cola solution to yellow, with dark precipitate at the bottom of the flask, although chemically the drug appeared to be stable for 24 hours. Nevertheless, because of a lack of palatability, Coca-Cola should also not be used to dissolve imatinib.

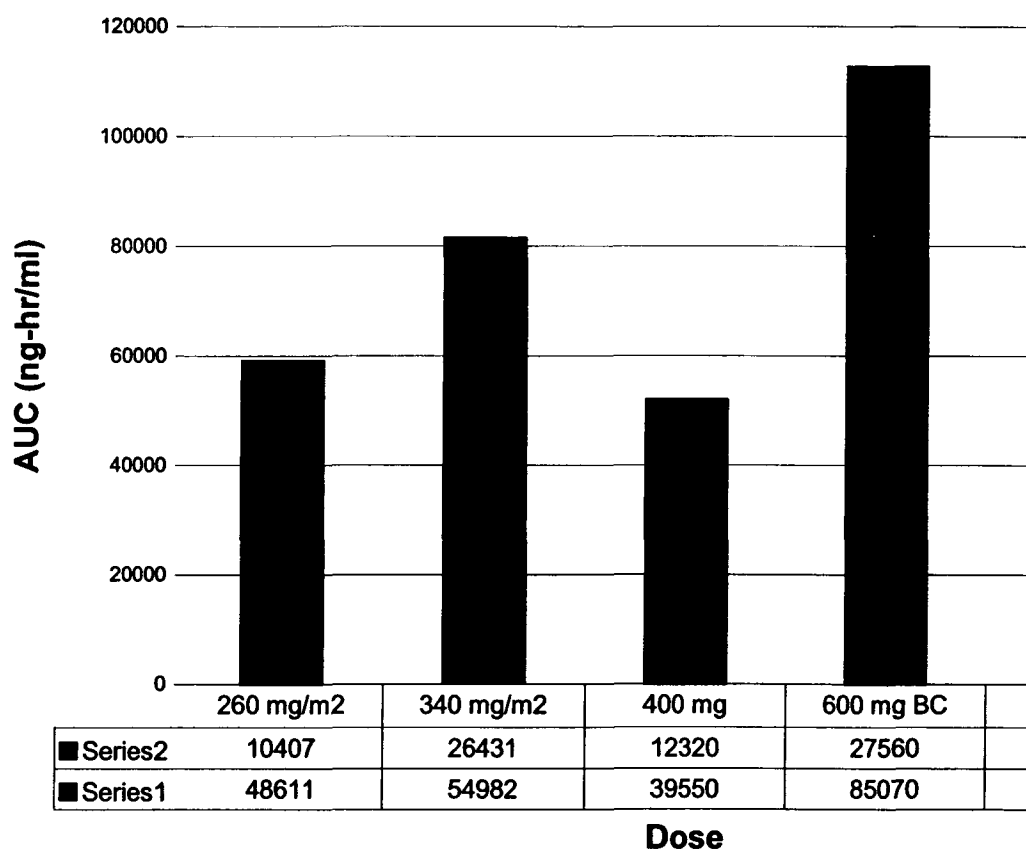
#### **H. Was the correct dose administered ?**

There was no apparent dose-response relationship seen in the pediatric population. There was considerable overlap in AUCs among the doses given to the children. The pediatric doses of 260 mg/m<sup>2</sup> (400 mg/1.73 m<sup>2</sup>=260 mg/m<sup>2</sup>) and 340 mg/m<sup>2</sup> were chosen to reflect the effective doses in the adults, 400 mg and 600 mg. The AUC provided by the 260 mg/m<sup>2</sup> dose however is indistinguishable from the 340 mg/m<sup>2</sup> dose; both are similar to the AUCs produced by the adult 400 mg dose. It is not clear if a lower dose could have been used in the adult population, and it is also not clear if a lower (or higher) dose would have been equally effective and safe in children. The drug appears less toxic than standard chemotherapy, and appears to be effective from the point of view

of cytogenetic response, in the pediatric population so no change in the dosage recommendation is indicated at this time.

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## Relationship between Dose and AUC Children vs Adults



### I. What is the applicant's plan for the marketing of a 50 mg capsule strength?

The 50 mg capsule was approved by FDA for marketing based on data in the original NDA application. Patients in this pediatric study received the 50 mg capsule. There is no 50 mg capsule strength mentioned in the applicant's amended label. It is therefore unclear what the applicant's plans are for marketing this strength. It is necessary that this strength be available to children.

**Appendix 1. Proposed labeling**

**Gleevec (imatinib mesylate)**

**NDA 21-335 / S-003**  
**Annotated US Package Insert**  
**Pediatric CML**



18 pages redacted from this section of  
the approval package consisted of draft labeling

## **Appendix 2. Individual Study Synopsis**

### **1. Pediatric pharmacokinetic/pharmacodynamic study**

**Study Title:** A Phase 1, dose-finding study to determine the safety, tolerability, pharmacokinetic and pharmacodynamic profiles and to evaluate for anti-leukemic effects of STI571A in pediatric patients with Ph<sup>+</sup> leukemia.

**Study period:** February 26, 2000 to September 4, 2001

**Study Centers:** 23 centers; USA-21, Canada-1, Australia-1

**Study Formulation:** STI571 was supplied as 50 and 100 mg hard gelatin capsules for oral administration. The formulation control and batch numbers were as follows:

STI571	Formulation Control No.	Batch No.
50 mg	3752417.00.003	X3621199
	3752417.00.003	X0260100
100 mg	3752425.00.002	X3641199
	3752425.00.002	X0980700

#### **Objectives:**

##### **Primary:**

- To estimate the maximum tolerated dose (MTD)
- To determine the dose-limiting toxicity (DLT) of STI571 in children with recurrent  
Ph + leukemia
- To characterize the pharmacokinetic behavior of STI571 in this patient population

##### **Secondary:**

- To assess the antileukemic activity of STI517

#### **Study Design**

This was a Phase 1, open-label, multicenter, dose-finding study. STI571 was given orally, once daily or BID if the dose was  $\geq 800$  mg/d, with no interruptions in the absence of dose-limiting toxicities. Two 28-day courses were given and patients who were responding to therapy could continue the therapy in the absence of significant toxicities, and/or progressive disease. STI571 pharmacokinetic evaluations were performed during Course 1 on Day 1 and 8.

**Subjects:** male or female pediatric patients  $\leq 21.99$  years with Ph<sup>+</sup> leukemia, recurrent or refractory ALL or AML, or CML which was either recurrent after stem cell transplantation or resistant to  $\alpha$ -interferon therapy

**Pharmacokinetic sampling** was performed at:

- for QD dosing: 0.5, 1, 1.5, 2, 4, 8, 24, 48 hours (Day 8 only) post-dose
- for BID dosing: 1, 2, 4, 10, 12, 13, 16, 24, 48 hours (Day 8 only) post-dose

**Assay:** An \_\_\_\_\_ assay was used to measure imatinib and CGP74588 concentrations. Two \_\_\_\_\_ methods were used, \_\_\_\_\_  
\_\_\_\_\_ These assays were not cross-validated; however, the pharmacokinetic parameters derived from these plasma concentrations are not statistically significantly different from each other, and so these samples have been grouped together.

**Pharmacokinetic data analysis:** Non-compartmental PK parameters  $C_{max}$ ,  $t_{max}$ ,  $t_{1/2}$ , AUC<sub>0-24</sub>,  $V_z/F$ ,  $Cl/F$  and accumulation ratio were calculated from plasma concentration-time profiles using WinNonlin software.

## **Results:**

Subjects: 31 patients  $\leq 21.99$  years

Diagnosis: 15-chronic phase CML, 16-blast crisis CML or Ph+ acute leukemia

Assay: Coefficients of variation were acceptable.

Pharmacokinetic analysis: as presented in the review

**Reviewer's comments:** The study was appeared to be well planned and performed, and yielded valuable pediatric PK data. It is unclear which patients received capsules and which received a liquid preparation. This information may explain some of the PK variability in the data.

## **2. Dissolution experiments with imatinib**

**Title:** STI517 50 mg capsules: Report of compatibility tests with beverages

**Purpose:** To determine which liquids could be used to dissolve imatinib

### **Objective:**

- to assess the compatibility of STI571 with the following beverages:
  - Mineral water
  - Coca-Cola
  - Apple juice
  - Orange juice

### **Method**

Open 4 capsules (50 mg dosage strength) and quantitatively transfer their powder content into a 100 ml volumetric flask, carefully add 80 ml of the beverage and sonicate for 20 minutes.

Cool down to room temperature and fill to the mark with the same beverage.

For each time-point, take out 20 ml of the suspension without shaking and centrifuge at about 1500 g \_\_\_\_\_ for 10 minutes. Pipette 5.0 ml of the clear supernatant solution into a 20 ml volumetric flask and fill to the mark with solvent \_\_\_\_\_

Use this solution \_\_\_\_\_ STI571 / 1 ml) as the test solution for the Test Method, Assay and degradation products by \_\_\_\_\_

Carry out the same procedure for all conditions with each beverage without adding capsule powder and compare the resulting chromatograms for interference of any peak.

Acceptance criteria:

Table of Acceptance Criteria		Values of acceptance
Assay	start	— %
	4 hours	Not less than — below the start value
	24 hours	Not less than — below the start value
Degradation products	Each individual	— %
Degradation products	Sum	— %

#### Results:

**Mineral water:** ACCEPTABLE for 0 and 4 hour time points, not acceptable at 24 hours

**Coca-Cola:** acceptable for all time points BUT strong discoloration of the brown solution to yellow with precipitation of brown Coca-Cola ingredients and so  
**NOT ACCEPTABLE**

**Orange juice:** NOT ACCEPTABLE at any time point, possibly due to adsorption of drug onto fruit residues

**Apple juice:** ACCEPTABLE at all time points

**Summary:** Imatinib may be dissolved in water or apple juice to produce a palatable and stable solution.

#### Reviewer's Comments:

The method described for dissolving imatinib is not practical for parents.  
It is unclear if different brands of apple juice will give similar results.

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/s/

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